

**Apparatus and process for sterilization of liquid media by means of UV irradiation and short-time heat treatment**

5 This invention relates to a technique for reliable and product-saving UV irradiation and heat sterilization of fluid media, especially of liquids containing microorganisms and/or viruses (e.g. foodstuffs, milk products, fruit juice products, chemical or pharmaceutical products, viral vaccines, active substance or proteins produced by genetic engineering, active substances or proteins from transgenic animals or plants, and blood plasma, or products obtained from blood plasma). A common feature of  
10 irradiation with ultraviolet (UV) light and of treatment by heat is that the inactivation reaction is accompanied by undesired damage to the product, the extent of which damage must be minimized by means of suitable reaction techniques and structural measures.

15 The process of sterilization of fluid media is based on contemporaneous application of the two process steps of heat treatment and UVC (Ultraviolett radiation category C) treatment which, when used in combination, have synergistic effects which allow microorganisms and viruses to be killed in a manner which is particularly gentle on the product itself. The reactors used are helical flow channels with a limited dwell  
20 time spectrum for the product. The product channels are produced by drawing a spirally corrugated hose body onto a cylindrical pipe body which is heat transmitting and/or transparent to UV rays. To avoid cleaning which is difficult to validate, the helical reactors are constructed in such a way that, after the product has been treated, they can be replaced by new, precisely conditioned and sterilized reactors.

25 Sterilization of liquid media is an important precondition for the application of biotechnological production processes in the food industry and the pharmaceutical industry. The aim is to ensure reliable and extensive depletion of microorganisms and/or viruses while at the same time largely protecting the sensitive substances of value. The main areas of application of the sterilization processes are sterile  
30 fermentation operations, shelf-life extension by sterile or low-microbe packaging of foods, and the pharmaceutical suitability of biological active substances of human or animal origin, e.g. from organs or blood plasma. For the use of biological active

substances, the FDA requires a sterilization process subject to validation and comprising several virus inactivation steps based on different principles of action. Validation of the sterilization processes requires that the reactors and installations used are in an exactly specifiable state. Cross contamination between process batches  
5 must be ruled out.

An important criterion in protecting the product involves minimizing the time during which the product is exposed in the reaction zone. Since the average duration of treatment needed is defined by the particles passing most quickly through the  
10 reaction zone, reducing the duration of treatment requires an as far as possible uniform dwell time distribution within the product stream. The literature [US 2002 096648 A1, US 2003 049809 A1, VDI heat atlas] describes the especially favorable dwell time behavior in helical flow channels, which is caused by secondary flows (so-called Dean vortices) acting perpendicular to the direction of flow (Fig. 3b, (23))  
15 (24). As tests on inactivating a model virus have shown, it has been possible for the first time to obtain a uniform and precisely controllable treatment of product solutions. Each liquid element flowing through is guided into immediate proximity of the treatment source and thus exposed to the inactivating UV radiation or heat.

20 In addition to the improved through-flow, it has been found that the combination of the short-time heat treatment and UV treatment conducted under suitable conditions (temperature and UV irradiation dose) is particularly advantageous. By both process steps taking place in rapid succession (UV treatment of the product stream after heating and cooling, or UV treatment of the product stream before heating and  
25 cooling) or overlapping (heating of the product stream, UV treatment and cooling), an additional synergistic inactivation potential is induced. While giving the same inactivation success, this surprisingly leads to a reduction in the energy needed and thus to a decrease in product damage in the overall process. The application of the heat sterilization technique requires at least two reactors, one for the heating and one  
30 for the subsequent cooling. To keep the product temperature constant, a thermally insulated conduit can optionally be coupled in as a temperature-holding section between heating and cooling reactor. In the case of UV treatment being carried out within the thermal treatment, the UV reactor also serves as holding module.

### Summary of the invention

5 The subject of the invention is a continuous process for sterilization and, if appropriate, virus inactivation of fluid media, in particular of aqueous reaction media, by means of a combined application of a heat treatment and a UV irradiation treatment, characterized in that the heat treatment of the fluid media (i.e., "product") takes place at a sterilization temperature of 40° to 135°C and the irradiation takes place at an irradiation density of 5 to 300 W/m<sup>2</sup>.

10

The fluid media (product) being treated is preferably held at the sterilization temperature for up to 50 seconds.

15 The heating of the fluid media to the sterilization temperature and the cooling of the fluid media take place independently of one another within 0.1 to 10 seconds.

A process is particularly preferred in which the thermal treatment takes place in successive steps of heating, temperature holding, and cooling (3), and the UV treatment takes place in particular during the thermal treatment.

20

The thermal treatment is preferably carried out using high-performance heat exchangers which, with a k value of  $k > 1000 \text{ W/m}^2 \cdot \text{K}$ , permit a heating and cooling of the product stream in a time of 0.1 to 10 seconds.

25 A process is further preferred in which all or some of the treatment steps are carried out using pre-sterilized disposable reactors cleaned according to GMP (Good Manufacturing Practice).

30 A further subject of the invention is an apparatus for carrying out the process according to the invention, and which is comprised of at least a heat treatment reactor, if appropriate a temperature-holding section, a UV irradiation reactor and a cooling reactor, characterized in that the sterilization and/or inactivation chamber through which the fluid media (product) flows, at least of the irradiation reactor and

of the heat treatment reactor, is formed by a deformable, helical, profiled hollow cylinder which is drawn tight onto the wall of a rigid, straight, cylindrical support body transparent to the sterilization or inactivation energy used.

5 Detailed description

The deformable, helical hollow cylinder used is preferably a corrugated plastic hose which, for product delivery and discharge, is connected at both ends to distributor heads.

10

An apparatus is particularly preferred in which the distributor heads have tangential or preferably radial product delivery and discharge lines, free of dead space, in the area of the annular gap between distributor head and support pipe.

15 An apparatus is also preferred in which the distributor heads (9, 10) are worked from the hose ends by subsequent thermal deformation of the corrugated hose or are preferably made from a plastic material produced and worked by injection-molding and/or stretching, respectively, and are connected with a force fit to the cylindrically widened hose ends by means of an O-ring connection (32, 33) pressed on from the  
20 outside.

In a preferred embodiment, the corrugated hose has an outer jacket or a reinforcement for the connection.

25 The outer jacket is particularly preferably formed by a shrinkable plastic tube, a pipe pushed over the spiral hose, or preferably a two-part, cylindrical shell, the reinforcement being formed by a steel or plastic coil.

The UV irradiation reactor preferably has, as energy source, one or more UV  
30 emitters as energy source in the cylindrical support body, and the support body is preferably made of a material transparent to UV light, e.g. quartz glass, and if appropriate has a corrugated plastic hose.

An apparatus is further preferred in which windows (64) for observing the UV energy radiated into the product are formed in the distributor heads (9, 10), which windows (64) are sealed in the distributor heads (9, 10), in particular via an O-ring connection (31, 64).

5

In a particularly preferred design, UV sensors are built into the distributor heads for the purpose of detecting the UV radiation intensity radiated into the product chamber.

- 10 The heat treatment reactor particularly preferably has a pipe formed of a heat transmitting material, for example stainless steel, like 316L or V4A, Chromium-Nickel steels and austenitic steels, for the support pipe, and a corrugated hose made of plastic. Plastics useful for this purpose are Polytetrafluorethylene (PTFE), Perfluoroalkoxypolymers (PFA), FEP (Copolymers from Hexafluoropropylene and  
15 Tetrafluoroethylene), PVDF (Polyvinylidene fluorides), ECTFE as well as Polypropylenes and Polyethylenes.

- In order to increase the heat transfer of a temperature control media flowing through the reactor, an insert element is preferably incorporated in the centre of the support  
20 pipe of the heat treatment reactor so as to narrow the cross section, and provide for the flow of temperature control medium through the support pipe.

- The insert element narrowing the cross section can also preferably have terminal flange connections which are connected releasably by means of a thread or  
25 preferably a bayonet closure and seal off the inner space of the support pipe.

A design is particularly preferred in which the insert element has a radial distributor for the heat transfer medium.

- 30 The insert element particularly preferably has a helical inner contour.

A further preferred design of the apparatus is characterized in that the support pipe (62) is closed at one end and has, at the other, open end of the support pipe, an insert element with inlet and outlet line for the heat transfer medium.

- 5     The insert element is particularly preferably in the form of a flanged pipe in which the heat transfer medium inlet line is connected to the pipe interior and the outlet is via the gap between insert element and support pipe.

- 10    In a preferred variant, an electrical resistance heating source, which is inserted into the support pipe (63), is arranged in the heat treatment reactor.

- 15    In a preferred embodiment, in order to improve the heat conductivity of the annular gap between heating source and support pipe, the annular gap is filled with a heat transfer medium.

- 20    A further preferred variant of the apparatus is characterized by a receiving vessel connected to the support pipe, for collection of the heat transfer fluid which displaced into the support pipe upon insertion or operation of the heating source.

- 25    In the area of its inlet and outlet, the heat treatment reactor particularly preferably has temperature sensors, e.g. PT100 platinum resistance sensors, for determining the heat transfer medium temperature and/or the product temperature.

- 30    A design of the apparatus is also particularly preferred in which the sensors are connected to flow regulators for the heat transfer medium stream and/or the product stream.

#### Brief description of the drawings

- 35    Figure 1a illustrates a block diagram of the process of the invention, wherein the product is first subjected to the heat treatment step, then, following passage through the holding section is cooled and then subjected to the ultraviolet treatment step..

Figure 1b illustrates a block diagram of the process of the present invention wherein the ultraviolet irradiation step is followed by the heat treatment step.

Figure 2 illustrates a block diagram of the process of the present invention wherein the product is cooled immediately after the ultraviolet irradiation treatment, without first passing through a holding section.

Figure 3 illustrates a reactor with helical channels according to the invention.

Figure 3a illustrates a reactor according to the invention, having a sheath 21 over the corrugated hose forming the helical channels.

Figure 3b illustrates a cross-section of a channel of the reactor, with contact point 22 enlarged.

Figure 3c illustrates a cross-section of a channel of the reactor, formed with a corrugated hose having metal reinforcements 50.

Figure 4 illustrates a UV irradiation reactor having a corrugated hose 5 over a UV-transparent support pipe 65, made of quartz glass, and UV emitter 25 installed in support pipe 65, with quartz windows 64 and UV sensors 26 & 27.

Figure 4a illustrates an enlargement of the bottom part of the UV irradiation reactor of Figure 4, showing distributor head 9 having an o-ring seal 33

Figure 5 illustrates a thermal treatment reactor according to the invention, having support pipe 34 formed of a heat-transmitting material with flange connections 36, 46 for heat transfer media.

Figure 5a illustrates an insert made of a two part cylinder 35, 43, the parts of which can be connected to each other with a force fit by a bayonet closure 44, 45.

Figure 5b illustrates a cutaway of a reactor having the insert of Figure 5a with the two parts connected to each other

5 Figure 5c illustrates an insert element 48, which when inserted into the support pipe of the thermal treatment reactor of the invention forces the heat transfer media to follow a helical path 49.

Figure 6 illustrates a thermal treatment reactor of the invention having a lance 52 through which heat transfer media can be conveyed to a closed end of support pipe 62, whereby the heat transfer media will then be introduced into the annular gap 47 to flow back up to outlet 51.

Figure 7 illustrates the heat treatment reactor of the invention having an electrical heating source 57.

15

**Examples:**

As is shown in Figures 3, 3a and 3b, reactors with helical channels (8) are used according to the invention as the apparatus for carrying out sterilization and virus inactivation. The channels are produced by drawing a helical hose (5) onto a cylindrical support body (6). By means of a suitable geometry of the corrugated hose (5), which has a slightly reduced internal diameter compared to the support body (6), a tight, force-fit connection between the two reactor elements is established. In this way, it is possible to prevent the axial short-circuit flows that would otherwise be caused by gaps between the flow channels, which, as tests confirm, would result in a considerable widening of the dwell time distribution. The product stream is expediently directed upwards in order to prevent back-mixing of the product stream through gas bubbles flowing in counter-current. Swelling of the corrugated hose (5) as a result of the pressure loss increasing in the case of larger product flows is undesirable because of the formation of short-circuit flows and is prevented, according to the invention, by a suitably dimensioned wall thickness of the corrugated hose (5) and/or by metal reinforcements inserted into the corrugated hose and/or by a sheath (21). The configuration of a jacket tube is in this case expediently



such that the internal diameter of the jacket is slightly smaller than the external diameter of the hose, in order to generate an additional contact pressure without appreciable hose deformation. In the case of small pressure losses, a shrinkable tube easily fitted onto the corrugated hose can improve the pressure stability. Other jacket constructions which could likewise be used after module production could be made for example of half-shells and multiple wound layers of glass fiber-reinforced plastic.

The energy input takes place via the protective pipe (6) which, for UV treatment (see Figures 4 and 4a), is designed as a quartz pipe (65) transparent to UV rays, and, for thermal treatment (see Figures 5, 5a, 5b and 5c), is designed as a thin-walled metal pipe (34) with good heat conductivity. In both sterilization methods, coatings form on those surfaces of the support pipe used for energy input. These coatings referred to as fouling can be cleaned off where the soiling is able to be brought into contact with a cleaning agent. In this context, parts which prove particularly difficult to clean are the areas (22) particularly susceptible to fouling around contact points between hose and pipe (see Fig. 3b). Complete dismantling of the reactor, which is necessary in this case for carrying out cleaning in accordance with GMP, cannot be done on site by the operators because of the large amount of time needed and the high degree of precision. For this reason, according to the invention the reactors are supplied as disposable modules which are packaged under sterile conditions and are quick and easy to replace and are recommended for use in GMP sterilization processes.

After the sterile packaging has been opened, and immediately before the process starts, the reactors are installed by connecting the identical attachment pieces (11, 12) present on the distributor heads (9, 10) to the attachment pieces (15, 16) of the product line. So-called triclamp connections, consisting of the correspondingly shaped flange ends of the attachment pieces (11, 12, 15, 16), a connection clip (17) and a special seal (18), are particularly suitable for rapid and hygienic connection.

The distributor heads (9) and (10) are connected in mirror-symmetrical arrangement to the cylindrically widened ends of the corrugated hose. A completely hygienic connection is preferably guaranteed by means of an O-ring seal (33, see Fig. 4a). In the seal illustrated in Fig. 4a, the connection between hose (5) and O-ring (33) is

obtained by pressing from outside by means of the ring (32). Other connection variants include welding the distributor heads to the corrugated hose, and integrating the distributor heads into the corrugated hose ends which have been modified by suitable, for example thermal, deformation. The distributor heads (9, 10) are sealed  
5 off with respect to the protective pipe (6, 65, 34) by means of O-rings (14).

In addition to supporting the reactor, the distributor heads (9, 10) have in particular the role of ensuring initial distribution of the product stream. The special design of the distributor heads ensures that it is possible to avoid any negative impact of the  
10 initial distribution on the dwell time characteristics. According to the invention, this is achieved by strictly limiting of the head volume contacted by the product, and this in turn by minimizing the gap width (28) and overall height (29). As dwell time studies show, by using distributor heads of minimized volume, it is generally possible to dispense with tangential delivery and discharge of the product stream in  
15 favor of a radial delivery which is preferable because of its easier and less costly production.

Figures 4 and 4a show the reactor provided for the UV irradiation. The support pipe (65) of the corrugated hose is made of UV-transparent quartz glass. One or more UV  
20 emitters (25) are installed in the centre of the support pipe (65) for UV treatment. To monitor fouling, the distributor heads (9) and (10) are equipped with quartz windows (64) through which it is possible for the UV sensors (26, 27) to measure the UV light emitted into the head space. According to the invention, the information provided by the sensors is used for GMP-compliant documentation of the irradiation procedure  
25 and for keeping the radiation dose constant by suitable adjustment of the product dwell time across the product throughput. In this way, the film formation (i.e., fouling) on the quartz glass and the loss of radiation capacity of the UV radiation source can be compensated for without affecting the irradiation procedure.

30 Figures 5, 5a, 5b, 5c, 6 and 7 show the reactors for sterilization by thermal treatment, which reactors can be used equally for heating and for cooling the product stream. The support pipe (34) is made of an FDA-approved material that is pressure-stable, very thin and has good heat transfer properties. For example, stainless steel pipes

afford good heat transfer conditions. By electropolishing the pipe surface directed towards the product, it is possible to reduce the tendency towards formation of fouling layers on the heating surfaces.

5 For heat sterilization, the modules are connected via flange connections (36, 37, 42) and (46, 41, 42) to heating media, for example steam or hot water, or, for cooling purposes, to cooling media, for example cold water or brine. While the temperature control liquids expediently flow through the reactors in an upward direction in order to prevent formation of gas pockets, it is preferable, when using steam as temperature control medium, for the through-flow to be in a downward direction, for removal of  
10 condensate. To improve the heat transfer both for heating and cooling, particularly when using liquids as heat transfer media, it is generally necessary to increase the speed at which the media flow across the heat exchange surface (34) by providing inserts (35) which narrow the cross section.

15

As Figures 5, 5a and 5b show, such an insert can be made up of a two part cylinder (35, 43) welded to the connection flanges (37, 41). The two cylinder elements (35, 43) can be connected to one another with a force fit by means of a thread or, in order to reduce the load on the O-ring during assembly, more preferably by means of a  
20 bayonet closure (44, 45). The centrally delivered heat transfer media (56, 51) are distributed via the radial bores (40) into the annular gap (47) between insert (35, 43) and support pipe (34) and are removed again at the opposite end via the bores (40) which are in a mirror-symmetrical arrangement. As Fig. 5c shows, instead of the cylindrical annular gap, it is possible for the insert element (48), in this case set  
25 closer to the wall of the support pipe, to be shaped in such a way as to force the temperature medium to follow a helical flow path (49) which, because of the secondary flows which arise, provides an additional contribution to improving the heat exchange.

30 In the reactor shown in Fig. 6, the liquid heat transfer media are conveyed through a lance (52) to the closed opposite end of the support pipe (62), where these media are introduced into the annular gap (47) through which they flow in the opposite direction. The handling of the temperature control modules is considerably simplified

in this way because, as a result of the flange (53) which can be integrated into the module, it is possible to dispense with the pre-assembly of the flange ends (37, 41) on the support pipe (34), as shown in Fig. 5. In addition, by moving the delivery and removal points of the temperature control media to the same end, the assembly work  
5 involved for installation in the production plant is reduced to securing a single flange connection (53, 54, 42). In the case of heat transfer media in the form of steam, the flow direction is reversed for condensate removal, so that the steam is first introduced into the annular gap (47) and flows downward through the latter before being flowing upwards, together with the condensate, through the lance (52). To  
10 avoid problems by having some condensate residing at the bottom, the bottom area is preferably either connected to a condensate drain or equipped with a demisting system.

In the arrangement shown in Fig. 7, indirect heating via flowing heat transfer media  
15 has been replaced by direct electrical heating via a cylindrical heating source (57). For this purpose, the heating source (57) is inserted into the support pipe (63) closed off at the opposite end. The poor heat transfer properties found even in the case of thin air-filled annular gaps (47) between heating source (57) and support pipe (63) can be avoided by filling with special heat transfer media (59). When using liquid  
20 heat transfer media in the vertically positioned support pipe, the liquid displaced upon insertion of the heating source (57) can be collected in the receiving vessel (58) connected to the support pipe.

#### Index List to the references in the drawings:

- |    |                                 |
|----|---------------------------------|
| 1  | fluid media                     |
| 2  | heating                         |
| 25 | 3 cooling                       |
|    | 4 UV irradiation treatment      |
|    | 5 corrugated helical hose       |
|    | 6 cylindrical support body      |
|    | 7 irradiation or heating source |
| 30 | 8 helical channel               |
|    | 9/10 distributor heads          |

	11/12	attachment pieces
	13	annular gap
	14	O-ring
	15/16	attachment pieces
5	17	connection clip
	18	seal
	19	fluid media inlet
	20	fluid media outlet
	21	sheath
10	22	contact point
	23	primary flow direction
	24	secondary flow
	25	UV emitter
	26/27	UV sensors
15	28	gap width
	29	overall height
	30	window
	31	O-ring seal
	32	connection ring
20	33	O-ring seal
	34	thin-walled metal pipe (heat transmitting)
	35	two part cylinder insert (top)
	36/37	flange connection
	38	O-ring
25	39	O-ring seal
	40	radial bores
	41	flange connection
	42	connection clamp
	43	two part cylinder insert (bottom)
30	44	bayonet closure (bottom)
	45	bayonet closure (top)
	46	flange connection
	47	annular gap

	48	insert element
	49	helical flow path
	50	metal reinforcements
	51	heat transfer media outlet
5	52	lance
	53/54	connection flange
	55	holding
	56	heat transfer media inlet
	57	electrical heating source
10	58	receiving vessel
	59	special heat transfer media
	60/61	temperature sensors
	62/63	support pipe
	64	(quartz) windows
15	65	UV-transparent quartz pipe